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4. TITLE AND SUBTITLE Myocardial Dysfunction Contributes to Irreversible Hemorrhagic Shock			5. FUNDING NUMBERS G N00014-96-1-1274	
6. AUTHOR(S) Kathleen H. McDonough, Ph.D., Harvey I Miller, Ph.D. Alastair H. Burns, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Grantee: Louisiana Board of Regents of Higher Education 150 Third St. Suite 129 Baton Rouge, LA 70801-1383 To: Kathleen H. McDonough, LSUMC, 1901 Perdido St. New Orleans, LA 70112			8. PERFORMING ORGANIZATION REPORT NUMBER 410-22-4111 linked to 410-22-6121	
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13. ABSTRACT (Maximum 200 words) We have performed a study of the effects of different time periods of hemorrhagic shock on isolated heart function of guinea pigs. In vivo hemodynamics were monitored during hemorrhage, shock and resuscitation and then intrinsic function of the heart was assessed. Three time periods were studied - 1, 2 or 3 hours of shock. In some animals shock lasted for 1 hour and then guinea pigs were resuscitated with whole blood or dextran 70,000 MW (same volume as the blood that was removed). The data collected from the isolated heart indicated that hemorrhagic shock lasting 1, 2 or 3 hours by itself did not cause major dysfunction of the heart. The only change in heart function that seemed to occur was in the 3 hour shock group in which the left ventricular compliance was slightly depressed. In animals that had been resuscitated with whole blood or with 6% dextran, ventricular performance was depressed compared to control hearts and compared to hearts from animals in hemorrhagic shock suggesting that reperfusion contributed significantly to myocardial dysfunction resulting from hemorrhagic shock.				
14. SUBJECT TERMS Hemorrhagic shock, myocardial function, resuscitation			15. NUMBER OF PAGES 10	
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ANNUAL PROGRESS REPORT

GRANT #: N00014-96-1-1274

PRINCIPAL INVESTIGATOR: Kathleen H. McDonough (e-mail: Kmcdon@LSUMC.edu)

INSTITUTION: Louisiana State University Medical Center

GRANT TITLE: Myocardial Dysfunction Contributes to Irreversible Hemorrhagic Shock

REPORTING PERIOD: 1 September 1996 - 30 June 1997

AWARD PERIOD: 1 September 1996 - 30 September 1999

OBJECTIVE: To investigate the effects of hemorrhagic shock on the myocardium and to determine if myocardial dysfunction contributes to irreversibility of hemorrhagic shock.

APPROACH: Guinea pigs are anesthetized and a thermistor probe is placed in the carotid artery, and polyethylene catheters are placed in the other carotid artery for measurement of blood pressure and sampling of arterial blood and into the right atrium via the jugular vein for delivery of cold saline for estimation of cardiac output.

When the instrumented guinea pigs begin gaining weight (approximately 2 days after surgery), animals are weighed and 50% of their blood volume (estimated as 6% of their body weight) is removed at a rate of 1 ml/min. Blood pressure, heart rate, cardiac output, body temperature, and blood glucose and lactate are measured at regular intervals. Animals are maintained in shock for 1, 2 or 3 hours or animals are resuscitated with whole blood after 1 hour of shock and then myocardial performance is assessed on isolated hearts. Hearts are removed after induction of anesthesia with pentobarbital and are studied in the isovolumic mode. Ventricular function curves are generated by changing left ventricular balloon volume and measuring left ventricular systolic and diastolic pressure, heart rate and coronary flow. Left ventricular response to increasing pacing rate from 3 beats per sec to 7 per sec is also assessed.

ACCOMPLISHMENTS (last 5 months): We have performed a study of the effects of different time periods in hemorrhagic shock on isolated heart function. In vivo hemodynamics were monitored during hemorrhage, shock, and resuscitation and then intrinsic function of the heart was assessed. Three time periods were studied - 1, 2 or 3 hours of shock. In some animals shock lasted for 1 hour and then guinea pigs were resuscitated with whole blood or dextran 70,000 MW (same volume as the blood that was removed). The data

collected from the isolated hearts indicated that hemorrhagic shock lasting 1, 2 or 3 hours by itself did not cause major dysfunction of the heart. The only change in heart function that seemed to occur was in the 3 hour shock group in which the left ventricular compliance was slightly depressed. In animals that had been resuscitated with whole blood or with 6% dextran, ventricular performance was depressed compared to control hearts and compared to hearts from animals in hemorrhagic shock suggesting that reperfusion contributed significantly to myocardial dysfunction resulting from hemorrhagic shock.

SIGNIFICANCE: The impaired ventricular function as a result of resuscitation after 1 hour of hemorrhagic may result from injury not only from the shock state itself but also from the composition and volume of the resuscitation fluid as well as the reperfusion of tissues that were inadequately perfused during the hemorrhagic shock stage,

WORK PLAN (next 12 months): The objectives for this next year will be to assess the effects of different resuscitation fluids on myocardial performance. Specific efforts will be made to enhance recovery of myocardial performance by supplementing the resuscitation fluid with agents such as dichloroacetate which stimulates myocardial pyruvate dehydrogenase and enhances energy metabolism.

PUBLICATIONS AND ABSTRACTS (last 5 months): None

REPORT FORM 1: This form should pull from your publications or new data the most important accomplishment of the project in the last year. Fill out the two sections below minimizing jargon. Continue on the back if necessary and attach supporting data, even if in crude form. Include 3 copies of the form and attachments along with the other 2 components of the report.

NAME/INSTITUTION Kathleen H. McDonough, Louisiana St. Univ. Med Ctr. June, 1997

PROJECT HIGHLIGHT (attach supporting data)

In this model of hemorrhage, 50% of the estimated blood volume was removed at a rate of 1 ml/min and animals were followed for 1, 2 or 3 hr of shock or after resuscitation with the shed blood. The in vivo data on the accompanying table show the fall in mean arterial blood pressure, cardiac output and hematocrit and the increase in blood glucose and lactate throughout 0', 30', and 60' shock or 2 or 3 hr of shock. The 30' and 60' R values represent measurements taken in animals resuscitated with blood indicating that blood pressure recovered somewhat whereas cardiac output recovered completely, glucose and lactate remained elevated and hematocrit was still decreased 1 hr after resuscitation. Myocardial performance is shown in Table 1. The first three columns show the maximum left ventricular developed pressure (LVDP), and the ventricular volume and left ventricular end diastolic pressure (LVEDP) required for that LVDP. LVDP was decreased from control only in the two resuscitated groups. The next columns demonstrate the LVDP and LVEDP when hearts were paced at 210 and 420 beats per min. In the two resuscitated groups, myocardial function was depressed compared to control. The 1 hr and 2 hr shock groups were not different from control suggesting that shock itself (at these time periods) did not cause myocardial dysfunction but rather reperfusion after shock caused myocardial dysfunction.

MAJOR PROBLEMS: (Sample: late receipt of funds, loss of personnel, technique doesn't work, etc.)

Funding for this research was received by the investigators in February, 1997 although funding was effective September 1, 1996 from Office of Navy funds and July 1, 1996 from Louisiana Board of Regents matching funds. Substantial progress was made between February and June since several individuals (technician and medical student) who were not paid from the grant assisted in the experiments.

POTENTIAL PATENTABLE INVENTIONS: None

Table 1. Performance of Isolated Hearts from Hemorrhaged Guinea Pigs

	Maximum LDVP (mmHg)	Volume at max LVDP (ml)	Paced at 3.5 Hz			Paced at 7 Hz			Intrinsic HR BPM	CF ml/min
			LVDP (mmHg)	LEVDP (mmHg)	LVDP (mmHg)	LVDP (mmHg)	LVDP (mmHg)	LVDP (mmHg)		
Control (n=6)	116±4	.271± .018	98±3	3±0	70±3	8±1			180±12	25.2±1.8
1 hr Shock (6)	117±5	.275± .019	101±8	2±1	63±5	13±5			163±11	26±2
2 hr Shock (6)	116±9	.258± .024	95±8	4±0	71±8	10±1			172±6	25.1± 2.2
3 hr Shock (6)	105±2	.225± .011	85±3	4±1	60±2	6±1			185±8	28±2
1 hr Shock/ 1 hr Blood Resuscitation (5)	91±3	.225 ±.036	68±8	3±1	45±5	12±2			188±15	27.2±1.6
1 hr Shock/ 1 hr Dextran Resuscitation (5)	85±7	.28± .038	78±8	3±1	45±7	16±3			153±22	25.3±1.2

Values are expressed as mean ± SEM. LVDP= left ventricular developed pressure; LEVDP= left ventricular end diastolic pressure; CF= coronary flow; HR= heart rate

Table 2. In vivo Parameters in Hemorrhaged Guinea Pigs

	Pre	0'	30'	60'	30'R	60'R	2hr HS	3hr HS
MABP mmHg	80±3	40±6	49±3	50±3	62±4	56±6	45±3	45±3
HR bpm	317±9	292±26	312±10	319±7	290±13	292±23	300±10	304±17
CO ml/min	164±15	59±23	134±14	116±13	171±29	176±33		
Glucose mg/dl	98.5±1.7	174.9± 8.1	177.4±8.8	160.6±7.7	158±14	139±11	125.8±9.4	106.8± 16.4
Lactate mg/dl	8.8±.9	51.1± 8.0	40.3±6.6	27.6±3.1	26.1±3.7	17.2±8.6	23.1±4.2	34.7±15.5
hct %	37.4±.6	29.5±.7	30.3±6.2	23.8±.5	26.1±3.7	26.5±3.4	21.7±.7	19.4±2.2

Values are expressed as mean ± SEM. Pre= before hemorrhage; MABP= mean arterial blood pressure; HR= heart rate; CO= cardiac output; hct= hematocrit; HS= hemorrhagic shock; R= resuscitation
Hearts from resuscitated animals were studied after 1 hr shock plus 1 hr resuscitation.

FORM 2--ANNUAL REPORT QUESTIONNAIRE, CALENDAR YEAR 1997
(for ONR use only- submit 1 copy)

Principal Investigator Name: Kathleen H. McDonough

Institution: Louisiana State University Medical Center

Project Title: Myocardial Dysfunction Contributes to Irreversible Shock

Number of ONR supported

Papers published in refereed journals: 0

Papers or reports in non-refereed publications: 0

Books or book chapters published 0

Number of ONR supported inventions/patents or licensed technologies:

Disclosed: 0

Filed: 0

Granted: 0 Patent No(s):

(describe in detail on Form 1)

Number of seminars/presentations

Invited: 0

Contributed: 0

Trainee Data (for those receiving full or partial ONR support):

	TOTAL	FEMALE	MINORITY	NON-US CITIZEN
No. Grad. Students:	1	1		
No. Postdoctorals:	0	0		
No. Undergraduates:	0	0		

AWARDS/HONORS TO PI AND/OR TO MEMBERS OF PI'S RESEARCH GROUP (please describe): None

No. of animals used; each species: 100 guinea pigs

Foreign collaborations (investigator, institution, location, objective)
None